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EDITORIAL COMMENT

Abnormal Heart Rate Responses to Exercise Predict Increased Long-Term Mortality Regardless of Coronary Disease Extent

The Question Is Why?*

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Several investigators have established that chronotropic incompetence *during* exercise and an abnormal heart rate (HR) response *after* exercise are associated with increased long-term mortality (1–7). The relationship persists even after adjustment for atherosclerotic risk factors, exercise-induced ischemic ST-segment depression, and in the case of abnormal heart rate recovery (HRR), Duke treadmill score. What is less well established is if the different exercise-induced HR parameters can predict mortality even after one considers coronary anatomy and left ventricular (LV) function, two major predictors of long-term outcome in patients with coronary disease.

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In normal subjects during progressive treadmill exercise, cardiac output is increased through an augmentation in HR and stroke volume. The increased HR response is mediated in part by withdrawal of vagal tone, increased sympathetic tone, and circulating catecholamines. Immediately after exercise vagal tone is restored, and the HR usually returns to baseline within minutes. However, in some patients, the autonomic balance that governs the HR response during or after exercise is disturbed, resulting in an inability to use most of the HR reserve during exercise (chronotropic incompetence) or an inability to promptly slow the HR immediately after exercise (abnormal HRR). Common definitions of an abnormal HR response *during* exercise are either an abnormal chronotropic index (%HR reserve/%metabolic reserve <0.8 in the absence of beta-blocker therapy) or an inability to reach 85% of age-predicted maximum (1). Abnormal HRR is usually defined as an HR that declines $\leq$12 beats/min in the first minute *after* exercise for protocols that use a post-exercise cool-down or $\leq$18 beats/min in the first minute post exercise for protocols that stop exercise abruptly (2,5,8). The cut-points for an abnormal HRR vary somewhat by institution (5). Patients with abnormal HR response during or after exercise are likely to be older, and have a history of hypertension, diabetes, chronic obstructive pulmonary disease, myocardial infarction, and are more likely to be taking vasodilator drug therapy.

In this issue of the *Journal*, Vivekananthan et al. (9) explore the hypothesis that abnormal HRR can predict total mortality even after accounting for the Duke coronary angiographic prognostic severity index. In a cohort of 2,935 patients from the Cleveland Clinic who underwent symptom-limited exercise testing and had coronary angiography within 90 days, 29% had abnormal HRR, 14% had severe coronary artery disease (CAD), and 11% of the patients died after six-year follow-up. Abnormal HRR was defined as $\leq$12 beats/min during the first minute after exercise using a 2-min post-exercise cool-down at 1.5 mph and 2.5% grade, except in patients having an exercise echo procedure where the cutoff was $\leq$18 beats/min during the first minute after abrupt cessation of exercise. After adjustment for CAD severity and LV function, an abnormal HRR remained predictive of six-year total mortality. The finding was consistent in men and women and was observed regardless of the post-exercise protocol performed (cool-down or abrupt cessation). The relationship persisted even after excluding patients with exercise-induced angina, ischemic ST segment depression, or poor functional capacity. There was no interaction between beta-blocker or calcium channel blocker use and the association of abnormal HRR with death. Furthermore, the authors report that an abnormal chronotropic index <0.8 in the absence of beta-blocker therapy was associated with increased mortality using Cox regression models even after adjustment for severe CAD, low ejection fraction, and abnormal HRR. The relationship to all-cause mortality was considerably stronger for an abnormal HRR than for an abnormal chronotropic index <0.8.

In a companion article in this issue of the *Journal*, Elhendy et al. (10) from the Mayo Clinic studied 3,221 patients referred for treadmill exercise echocardiography to determine if a low chronotropic index (<0.8) is predictive of death or myocardial infarction after adjustment for LV function and myocardial ischemia. The authors also examined the relationship of mortality to inability to reach 85% of age-predicted maximum (220 − age). Unfortunately, abnormal HRR results were not analyzed in this report. In the Elhendy series, patients using beta-blockers or those with atrial fibrillation, valvular heart disease, or previous coronary revascularization were excluded. Of 129 deaths during a median 3.2-year follow-up, 68% were non-cardiac. A low chronotropic index was observed in 25% of patients, and inability to reach 85% of age-predicted maximum was observed in 15% of patients. In the initial multivariate model, the most important predictors for total mortality were older age, male gender, low exercise workload, and

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exercise wall motion index. Chronotropic index and inability to reach 85% of age-predicted maximum were not selected as independent predictors of total mortality or cardiac death. When the two exercise HR variables were entered into an adjusted risk model, a low chronotropic index and inability to reach 85% of age-predicted maximum predicted mortality and cardiac death after adjustment for LV function and severity of exercise-induced myocardial ischemia. It is difficult to assess the magnitude of incremental information contained by the addition of both exercise HR variables to the adjusted model from the information provided by the authors. However, it would appear that in patients referred for an exercise echocardiogram similar to those enrolled in the study, the finding of a low chronotropic index or inability to reach 85% of maximum HR adds a small amount of incremental prognostic information over and above what is obtained from the exercise echocardiogram and pretest risk evaluation alone.

There are considerable differences in the patient characteristics and referral sources for both reports. In the Vivekananthan et al. (9) study, all patients had coronary angiography within 90 days of the exercise test, 28% had proximal left coronary disease, 27% had an ejection fraction <0.40, and 16% of the cohort were diabetic. In the Elhendy et al. (10) report, all patients were initially referred for an exercise echocardiogram, only 15% of patients had typical angina, and only 8% of the cohort were diabetic. In the Vivekananthan et al. (9) report, an abnormal chronotropic index was selected in the initial multivariate analysis in contrast to the Elhendy et al. (10) study where it was entered into an adjusted risk model. Nevertheless, the findings are consistent and indicate that even when LV function, exercise-induced myocardial ischemia, and functional capacity are accounted for, an abnormal chronotropic index during exercise <0.8 is associated with increased long-term mortality in both higher-risk (Vivekananthan et al. [9]) and lower-risk (Elhendy et al. [10]) patients referred for exercise testing. Furthermore, when abnormal HRR is present, it provides additive prognostic information to the angiographic severity of CAD that is more powerful than the chronotropic index.

In the Elhendy et al. (10) report, only 32% of patients died of cardiac causes. Vivekananthan et al. (9) only report total mortality. The exact cause of death is not reported in either series. This is unfortunate because the mechanism whereby an abnormal HR response to exercise predicts death is poorly understood. Abnormal HRR and CAD severity were independent predictors of all-cause mortality in the Vivekananthan et al. (9) series, and an abnormal chronotropic index and exercise-induced myocardial ischemia were independent predictors of mortality in both reports. This raises the intriguing possibility that the finding of an abnormal HR response is a surrogate for underlying autonomic dysfunction, and that the mechanism of increased mortality associated with this finding is more related to autonomic dysfunction than to the presence or extent of CAD per se. One could speculate that susceptible patients with dysfunctional autonomic HR responses may be more predisposed to lethal cardiac arrhythmias and thus increased mortality regardless of the presence or extent of CAD (11,12). More research into the causes of death would certainly be of interest, as would studies that determine the pathophysiologic mechanisms that produce the abnormal response in individual patients, that is, down-regulation of beta-adrenergic receptors, central nervous system effects, and the like. A better understanding of how abnormal exercise HR responses result in an increased death rate could lead to newer therapeutic approaches that reduce the mortality risk.

In most laboratories, failure to attain 85% of age-predicted maximum during exercise is considered to be a submaximal response, inadequate to sufficiently test cardiac reserve and associated with decreased sensitivity to detect CAD. The data from the Cleveland clinic and others demonstrate that an abnormal HRR is not diagnostic for CAD (5,9). Thus, in the clinical setting, abnormal HR responses should not be used to establish a diagnosis of CAD. However, that does not mean that an abnormal HR response invalidates the exercise test. The HR information obtained can be used to augment prognostic estimates because the findings provide supplemental information to the standard pretest evaluation and to the post-test findings of exercise-induced angina or ischemia and functional capacity.

Are abnormal HR responses ready for prime time today (i.e., routine use)? The evidence is mounting based on the results of well-done large patient series such as those published this month in the *Journal* as well as the results from earlier studies (1–10). I and others would still like to see more data from institutions with different referral patterns, in particular, symptomatic patients without previous revascularization referred for initial evaluation, the most common indication for exercise testing, to assess the generalizability of the HR findings (13,14). The most recent version of the American College of Cardiology/American Heart Association exercise test evidence-based guidelines, published in 2002, still recommends the Duke treadmill score for initial prognostic risk stratification (15). The Duke treadmill score incorporates exercise time, ST-segment deviation, and exercise-induced angina and works well in men but not as well in women or in the elderly (16,17). If a new tool such as abnormal HR responsiveness to exercise adds sufficient incremental information to impact management decisions, such as the need for coronary revascularization, pharmacologic therapy, or exercise training, it would be a welcome addition to the non-invasive assessment of patients with suspect CAD. Currently, we have no such data to support specific recommendations for any particular type of therapy in patients who manifest an abnormal HR response. Randomized medical or interventional trials that demonstrate reduced mortality with treatment may be a fruitful area for future research as more data come in and as

we develop a better understanding of the mechanisms that result in an abnormal HR response and how this leads to an increased risk of death.

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